CN 925/15 History

78 year old female.
FNA indeterminate lesion right thyroid lobe.
Previous THY1C (UK) Bethesda category 1 cyst fluid.
Ultrasound showed part solid/cystic changes, indeterminate in nature

Microscopic Findings

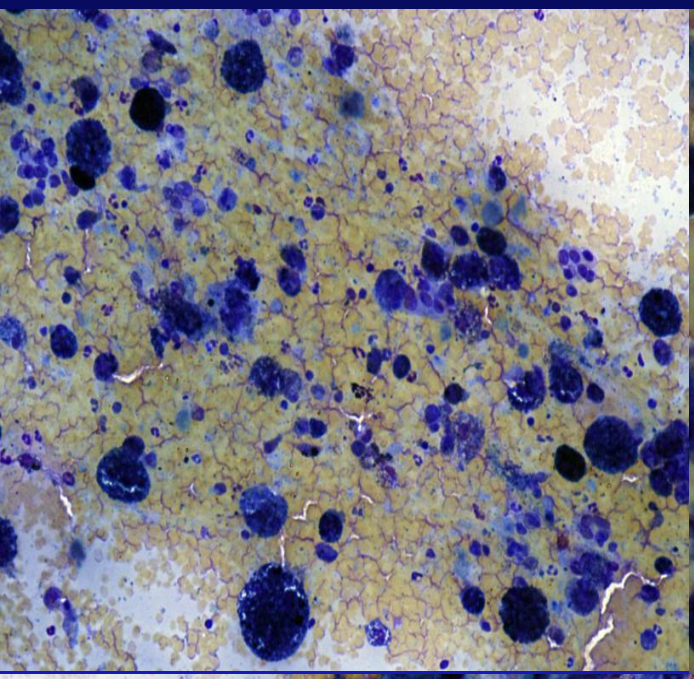
This aspirate shows features of a cystic lesion
Numerous macrophages are present
A population of thyrocytes shows oncocytic (Hurthle cell) change without nuclear features of papillary carcinoma.
This case was reported as a cystic lesion but with a subpopulation of cells of oncocytic appearance.
In the UK these lesions are classified as Thy3F *'neoplasm possible suggestive of follicular neoplasm'*. Elsewhere this would be regarded as an oncocytic follicular neoplasm of the thyroid, Bethesda class 4, *follicular neoplasm/suspicious for a follicular neoplasm-Hurthle cell (oncocytic) type.*

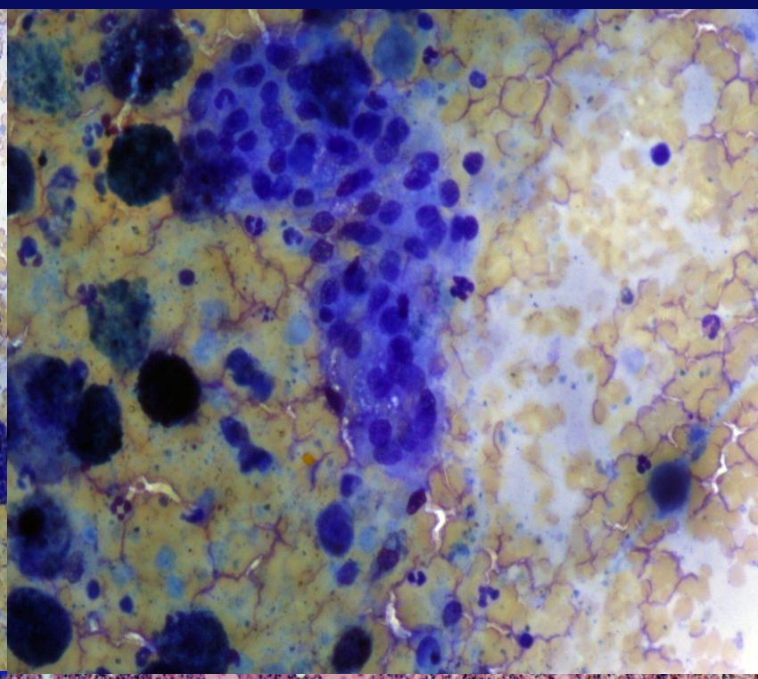
Learning Points

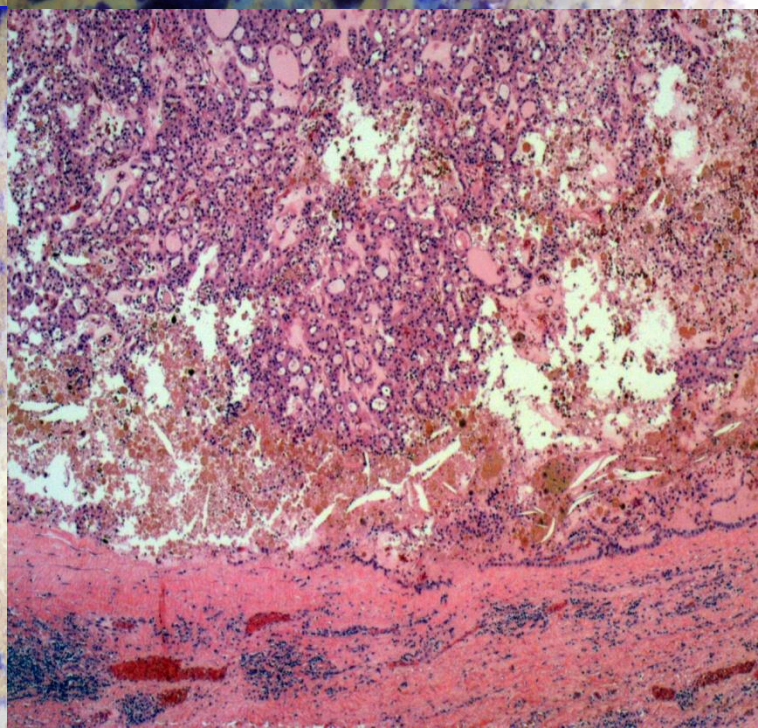
Oncocytic (Hurthle cell) thyroid lesions may be cystic.
There is some overlap of the features of oncocytic follicular lesions & papillary carcinoma on cytology, particularly in poorly prepared air dried Giemsa-stained preparations were the differential diagnosis may sometimes be problematic. Lesions of the thyroid on cytology with 'pink' cytoplasm may be papillary carcinoma so in some instances assessment of BRAF V600E mutation may be helpful as papillary carcinomas with pink cytoplasm on cytology usually show BRAF V600E mutation. BRAF V600E analysis was not performed in this case as it was quite clear that this is an oncocytic follicular lesion of the thyroid.

Case CN925/15

Blood, numerous macrophages & sheets of oncocytic cells but without nuclear features of papillary carcinoma indicating a partially cystic oncocytic follicular neoplasm of the thyroid







CN 1579/15 History

32 year old female.
FNA solid nodule in isthmus, U3, three months lump in the midline of the neck noticed after a viral illness by the patient.

Microscopic Findings

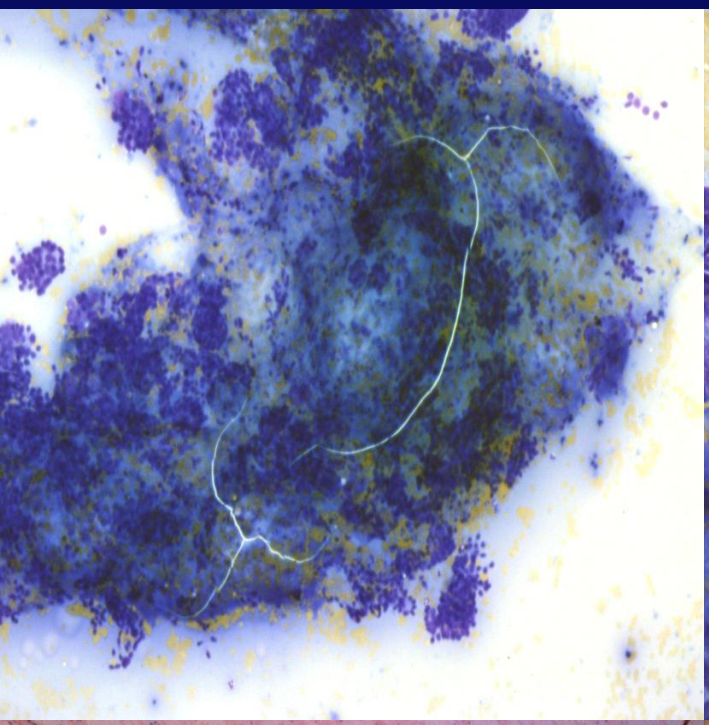
Sheets of follicular cells in a comparatively cellular aspirate forming microfollicles & without features of papillary carcinoma. There is some colloid present with cracking of colloid but this is a fairly typical example of a follicular neoplasm of the thyroid. In the UK these lesions are classified as Thy3F *'neoplasm possible suggestive of follicular neoplasm'*. Elsewhere this would be regarded as a follicular neoplasm of the thyroid, Bethesda class 4, *follicular neoplasm/suspicious for a follicular neoplasm'*

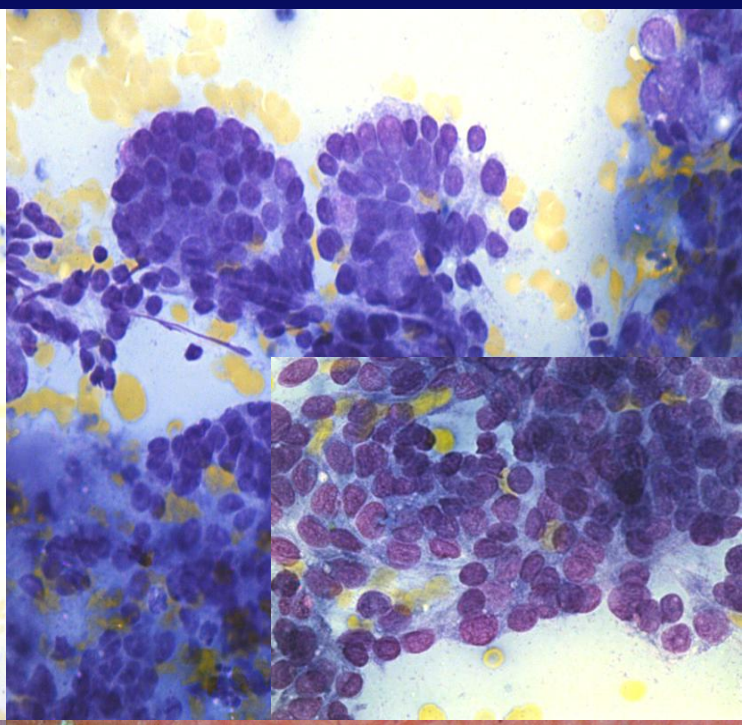
Learning Points

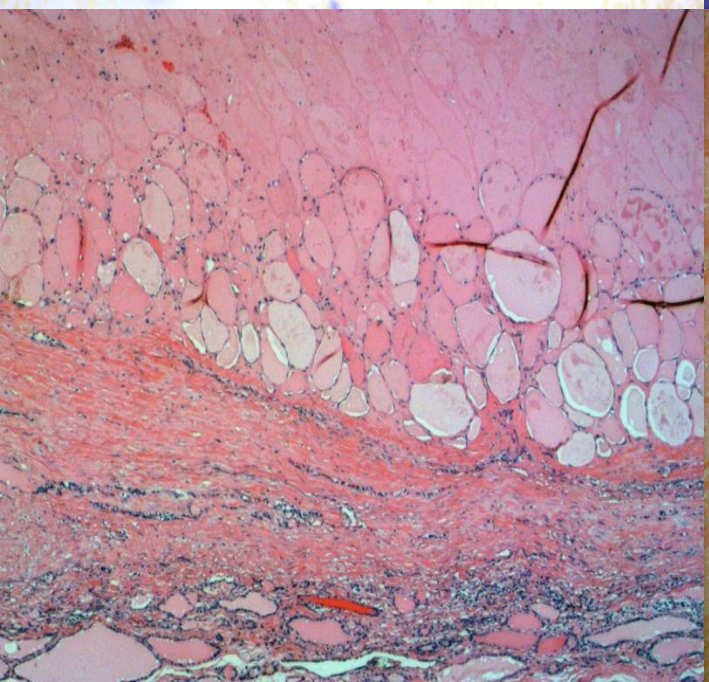
This is a fairly straightforward example of a follicular neoplasm of the thyroid on FNA cytology showing typical features. These lesions are typically RAS driven lesions & may show translocations of PAX8/PPARGγ and other mutations. With follicular lesions of the thyroid such as this the important cytological point is to ascertain that the nuclear features are not those of papillary carcinoma. In this case the cellularity of the lesion & relative lack colloid implies that the only diagnosis that can be entertained here is that of a follicular thyroid neoplasm.

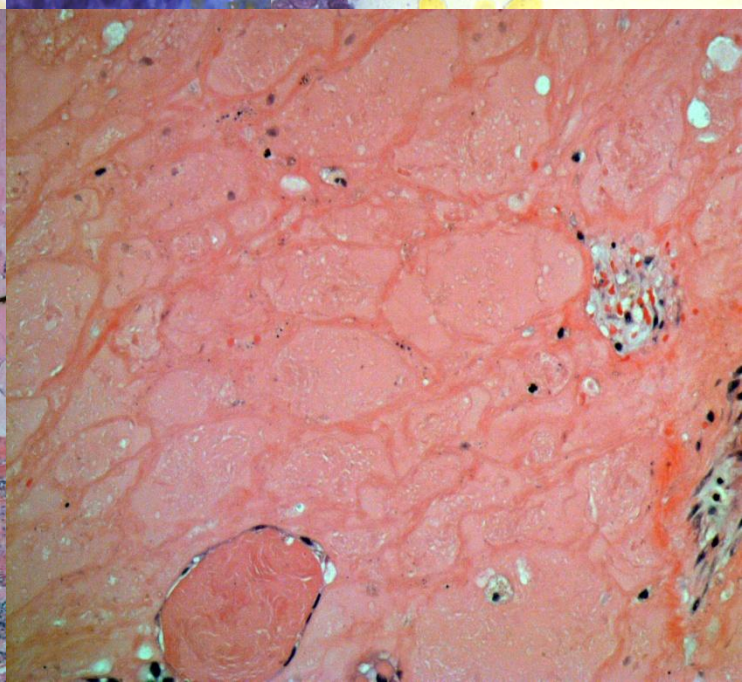
CN 1579/15

Sheets of follicular cells in a comparatively cellular aspirate forming microfollicles & without features of papillary carcinoma. There is some colloid present with cracking of colloid but this is a fairly typical example of a follicular neoplasm of the thyroid. Histology shows a follicular adenoma that has undergone partial infarction which is probably related to previous FNA.









CN 249/15 History

75 year old male.
FNA incidental left thyroid nodule in a goitre

Microscopic Findings

This aspirate is an extremely poor quality aspirate showing mainly blood apart from very few atypical cells which appear possibly degenerate and difficult to classify. Because at least 6 groups of 10 cells are present even though his aspirate is of poor quality it was felt that this aspirate should be regarded as indeterminate, THY 3a in the UK, elsewhere this would be Bethesda class III, atypia of undetermined significance.

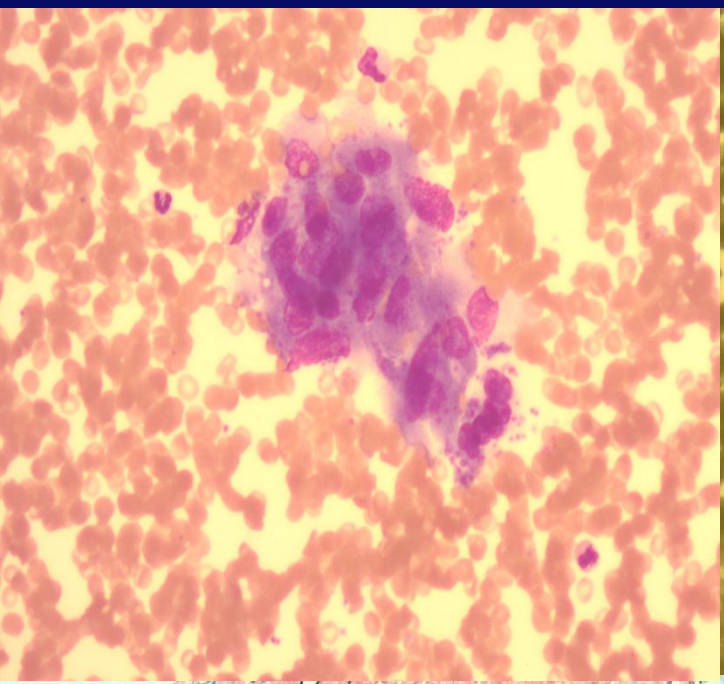
The needle core biopsy shows a slightly degenerate and hyalinised follicular nodule without evidence of papillary carcinoma or other lesion. With hindsight it would probably have been more appropriate to re-aspirate the nodule rather than proceed straight to a core biopsy.

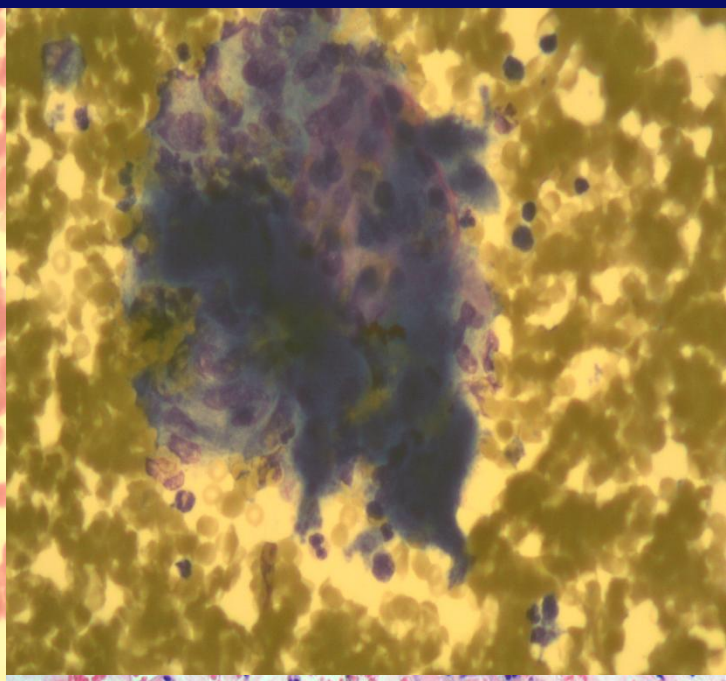
Learning Points

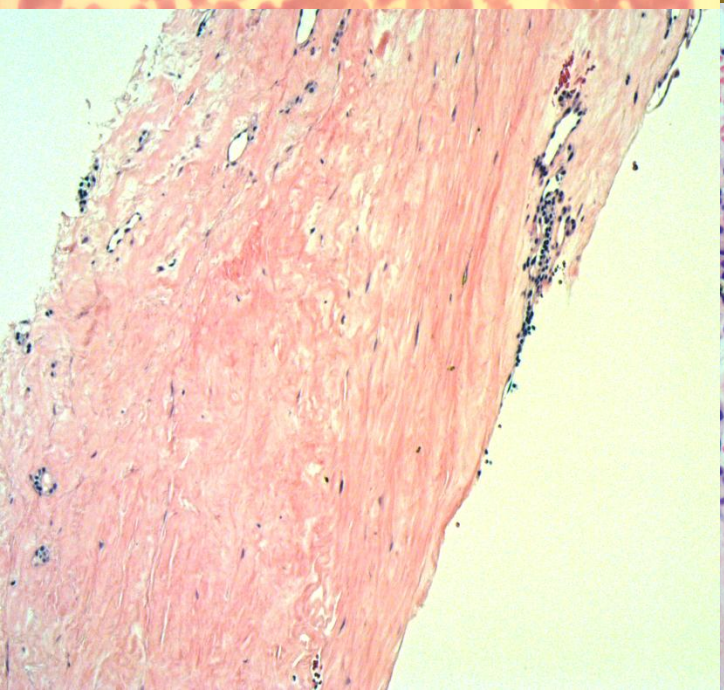
The role of core biopsy in the thyroid is still to some extent debatable but it is certainly useful for lesions which are difficult to aspirate or which produce a low cell yield and which on ultrasound are suspicious. It is also useful because it is much easier to perform immuno-histochemical stains on cell blocks from needle core biopsies. Our hospital undertakes needle core biopsies of thyroid lesions rather than undertaking open biopsies, particularly if a metastasis to the thyroid or some other unusual tumour is identified on FNA cytology and immunohistochemistry may be helpful. Other units have different policies on needle core biopsy.

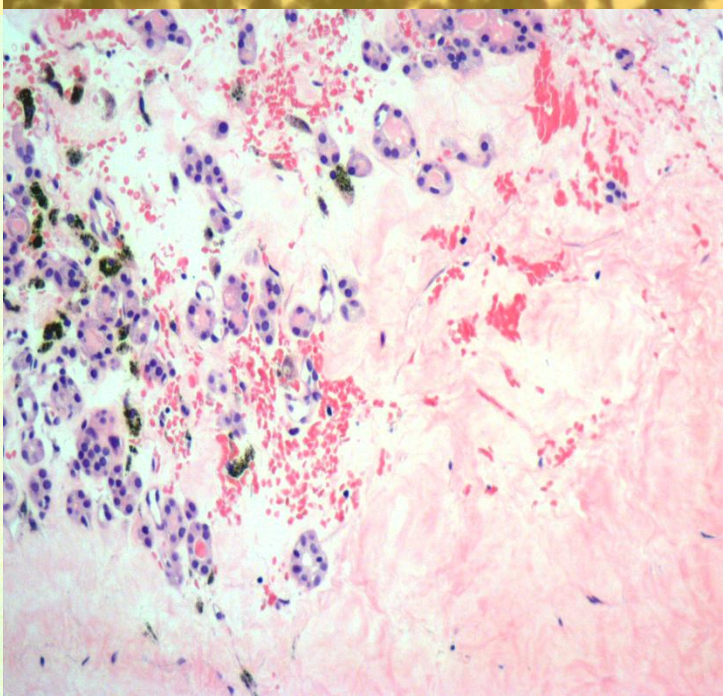
CN 249/15

This aspirate is an extremely poor quality aspirate showing mainly blood apart from a very few atypical cells which appear possibly degenerate and difficult to classify. Because at least 6 groups of 10 cells are present even though his aspirate is of poor quality it was felt that this aspirate should be regarded as indeterminate, THY 3a in the UK, elsewhere this would be Bethesda class III, atypia of undetermined significance. The needle core biopsy shows a slightly degenerate and hyalinised follicular nodule without evidence of papillary carcinoma or other lesion.



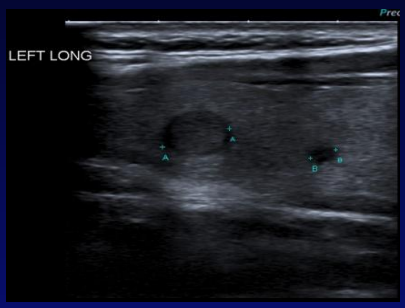






CN 7/15 History

38 year old female, multinodular goitre, increasing in size, 8x6mm peripherally hypervascular well-circumscribed nodule in left upper pole with microcalcifications with an adjacent 3mm hypoechoic nodule. No cervical adenopathy. FNA left upper pole nodule



Microscopic Findings

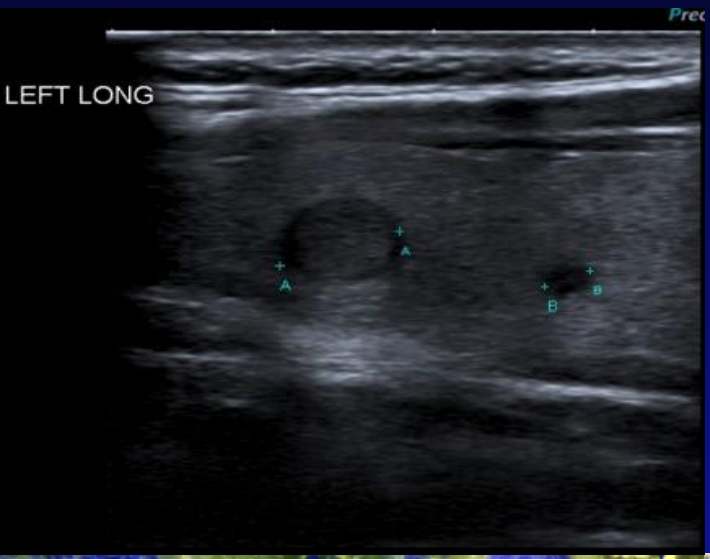
The larger nodule which was targeted shows sheets of oncocytes, with some colloid. Nuclear features of papillary carcinoma are not seen. This lesion showed no evidence of BRAF V600E mutation on FNA. In the UK these lesions are classified as Thy3F *'neoplasm possible suggestive of follicular neoplasm'*. Elsewhere this would be regarded as an oncocytic follicular neoplasm of the thyroid, Bethesda class 4, *follicular neoplasm/suspicious for a follicular neoplasm-Hurthle cell (oncocytic) type.* Histology shows an involuted circumscribed nodule corresponding to the area that was targeted by previous FNA. Infarction is relatively common post FNA of oncocytic lesions of the thyroid. The smaller lesion was a 5mm sized classical type papillary carcinoma pT1a, but this was not targeted so it is not seen in these preparations.

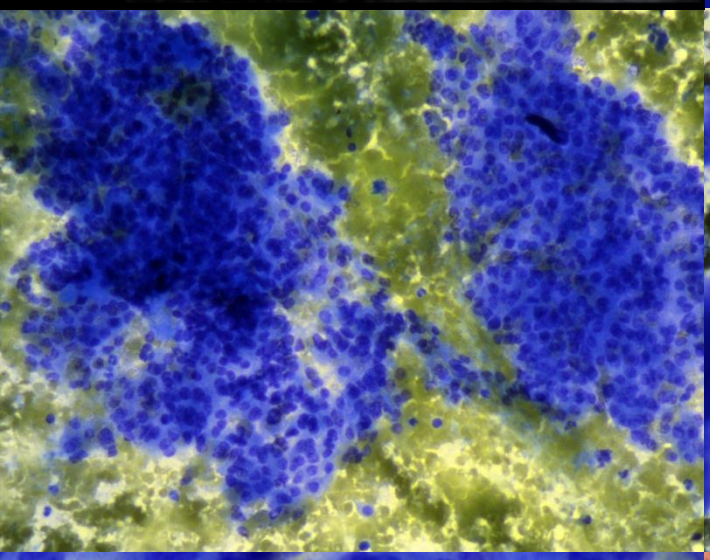
Learning Points

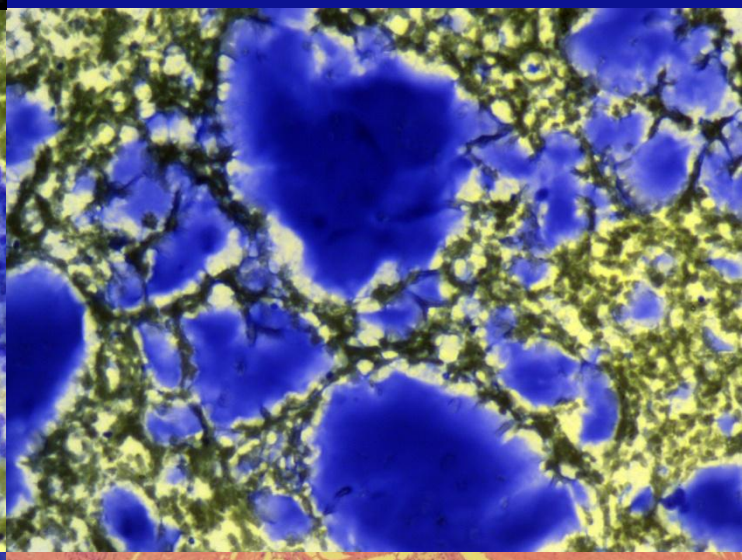
Oncocytic (Hurthle cell) thyroid lesions commonly undergo infarction after FNA. There is also some overlap of the features of oncocytic follicular lesions & papillary carcinoma Lesions of the thyroid on cytology with 'pink' cytoplasm may be papillary carcinoma so in some instances assessment of BRAF V600E mutation may be helpful as papillary carcinomas with pink cytoplasm on cytology usually show BRAF V600E mutation.

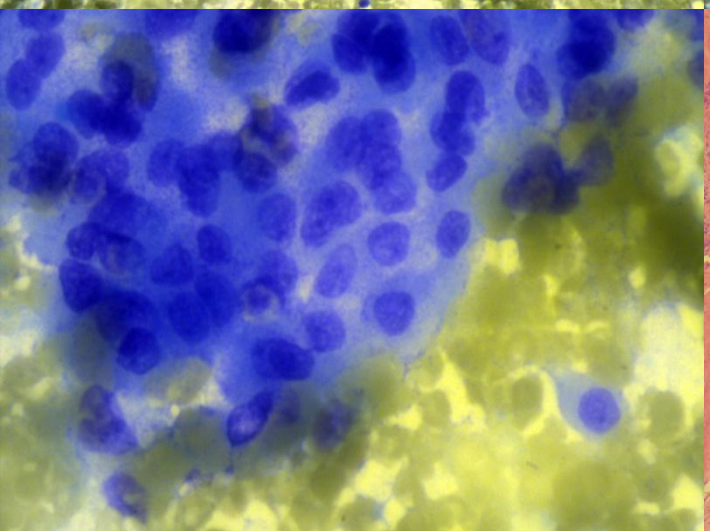
Case CN7/15

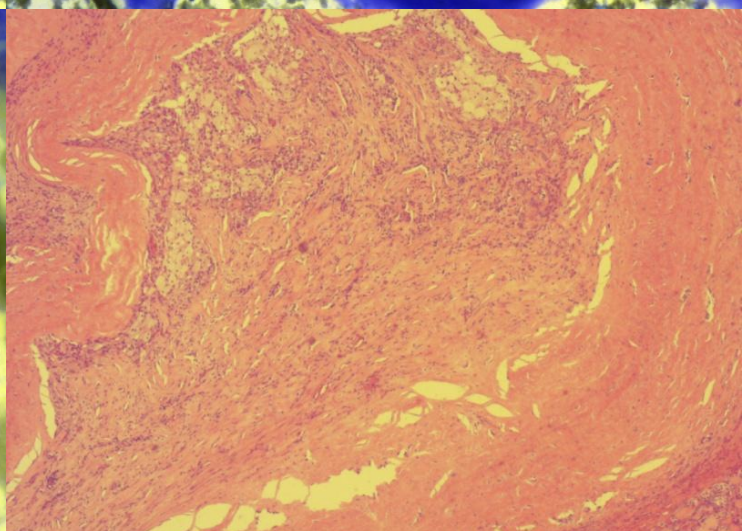
Sheets of oncocytic (Hurthle) cells with small amounts of hard colloid are present. The nuclear features are not those of papillary carcinoma.



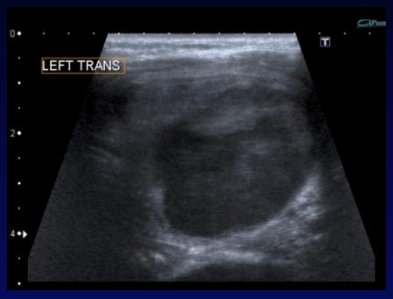








CN 113/15 History
40 year old female, heterogeneous hypoechoic solitary 37x35x52mm lesion within the left thyroid lobe, suspicious for neoplasm



Microscopic Findings

Sheets of hypercellular and monomorphic thyrocytes are present without colloid forming aggregates & sheets with nuclear hyperchromatism but without characteristic features of papillary carcinoma. This case was BRAF V600 E wild type. This was reported as Thy3F *'neoplasm possible suggestive of follicular neoplasm'*. Elsewhere this would be regarded as a follicular neoplasm of the thyroid, Bethesda class 4, *follicular neoplasm/suspicious for a follicular neoplasm.* The histology shows a thyroid tumour forming monotonous sheets and also some follicles. Vascular invasion is seen in the capsule. The nuclear features do show some clearing on histology & there are >3 mitoses/10HPF so although the nuclear clearing might suggest a syncytial variant of papillary thyroid carcinoma in this case because the features of papillary carcinoma were insufficiently developed a diagnosis of follicular carcinoma with some foci of poorly differentiated thyroid carcinoma was made.

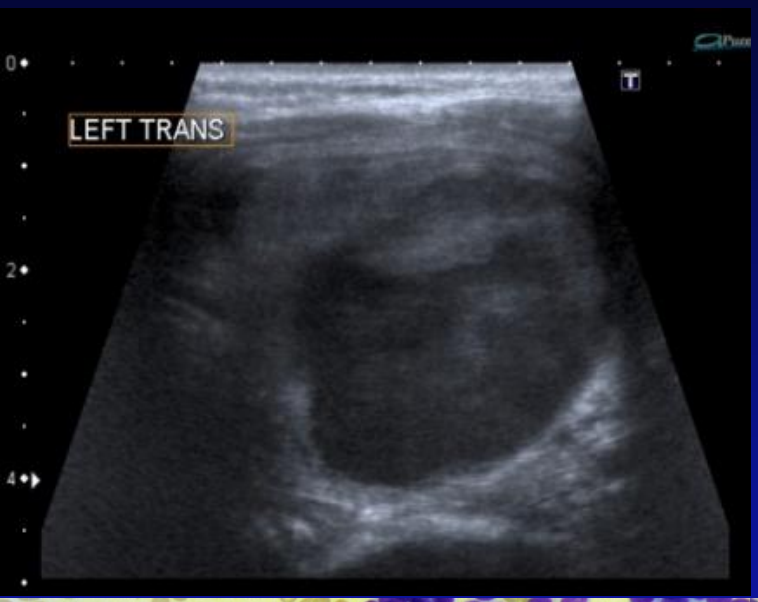
Learning Points

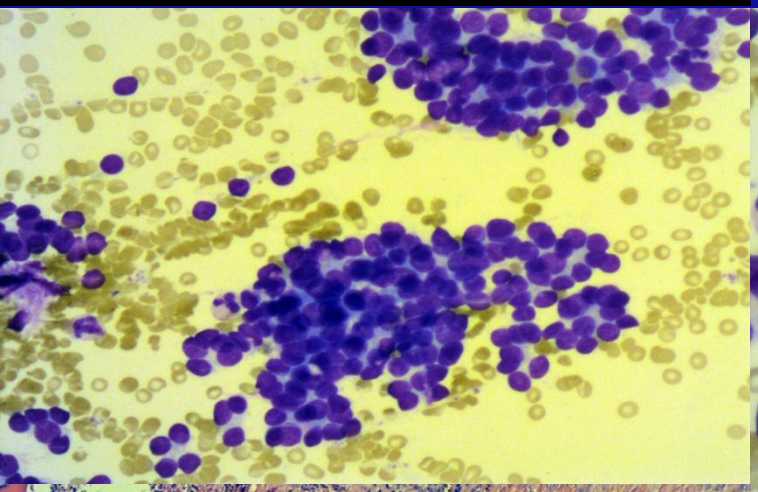
The diagnosis of more aggressive variants of follicular thyroid carcinoma and of poorly differentiated thyroid carcinoma on cytology may be problematic. In this case the tumour showed no evidence of BRAF V600E mutation. The appearances of poorly differentiated thyroid carcinoma on cytology can overlap with appearances seen in medullary carcinoma and also metastatic lesions to the thyroid. It would be unusual to make a confident pre-operative diagnosis of poorly differentiated thyroid carcinoma on cytology alone.

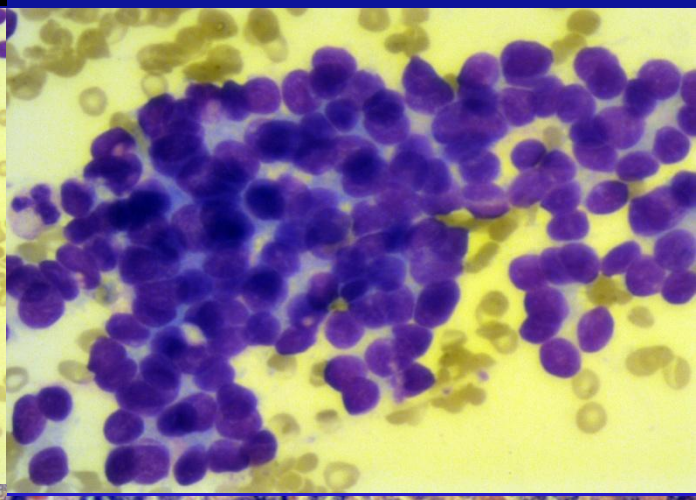
References
Bongiovanni M et al. Cytomorphologic features of poorly differentiated thyroid carcinoma. Cancer Cytopathol 2009;117:185-94
Barwad A et al. Fine needle aspiration cytology of insular carcinoma of the thyroid. Diagn Cytopathol 2011;40:E43-47
Pereira EM et al. Poorly differentiated carcinoma (insular carcinoma) of the thyroid diagnosed by fine needle aspiration (FNA) Cytopathology 1996;7:61-65

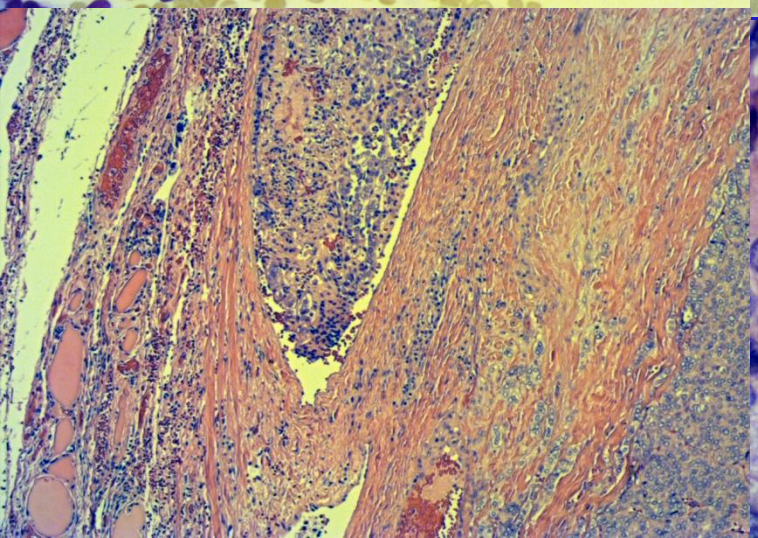
CN 113/15

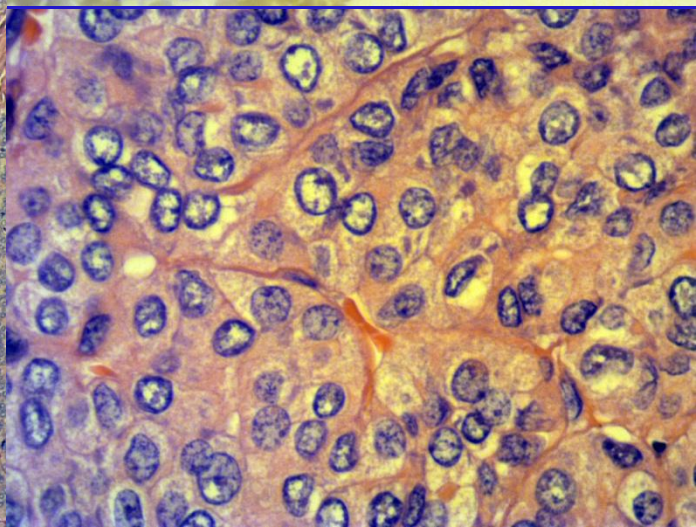
Hypercellular sheets of thyrocytes, without characteristic features of papillary carcinoma, no background necrotic material









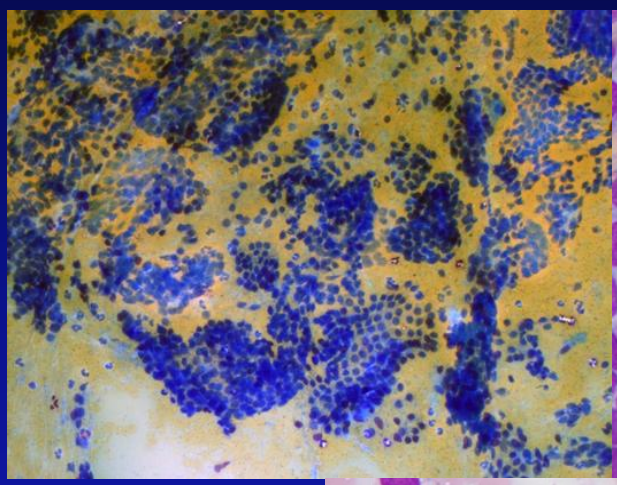
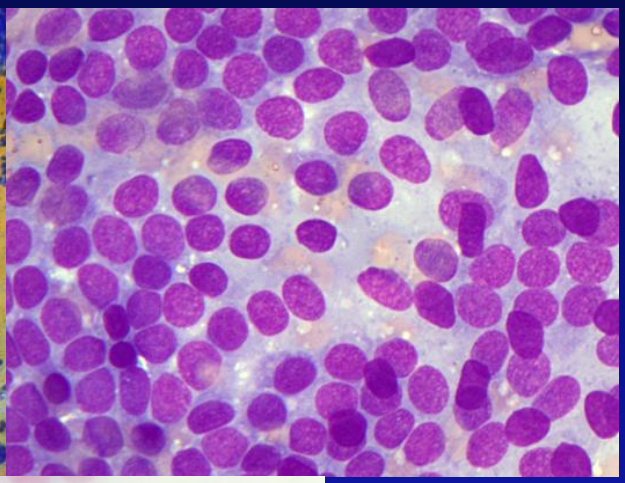
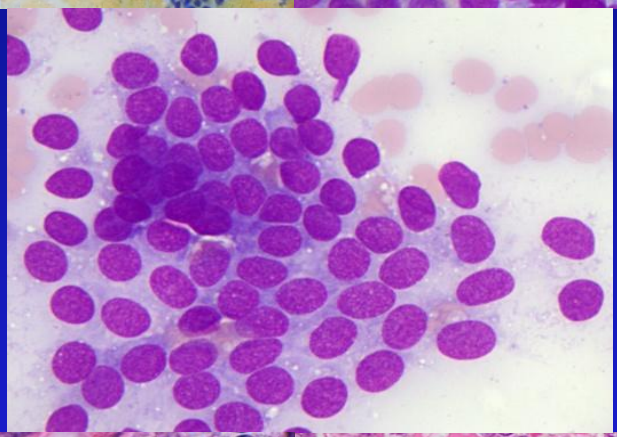
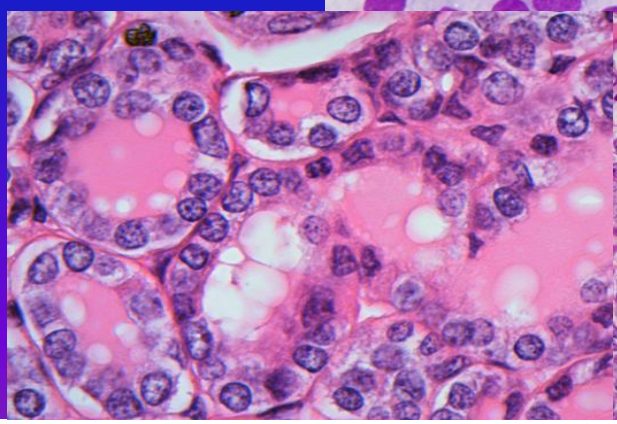
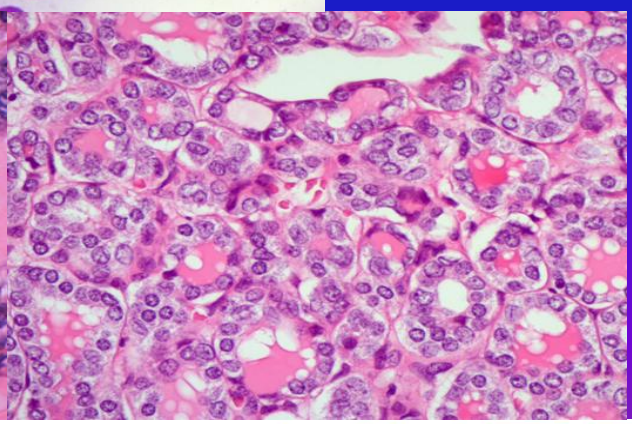


Case 6 CH 21784/16

History 58 year old female, 30mm nodule right thyroid, U3, FNA Thy3F, right thyroid lobectomy, 25mm well demarcated encapsulated lesion

Microscopic Findings

Comparatively cellular aspirate with groups of follicular epithelial cells, forming sheets & microfollicles, no definite intranuclear inclusions & no clear evidence of features of papillary carcinoma, no colloid, no psammoma bodies- appearances suggest a follicular thyroid neoplasm, UK Thy3F – neoplasm possible, TBSRTC Class IV

Diagnosis

NIFTP- Non invasive follicular thyroid neoplasm with papillary-like nuclei (Nikiforov YE et al JAMA Oncol. 2016 Aug 1;2(8):1023-9)

Learning Points

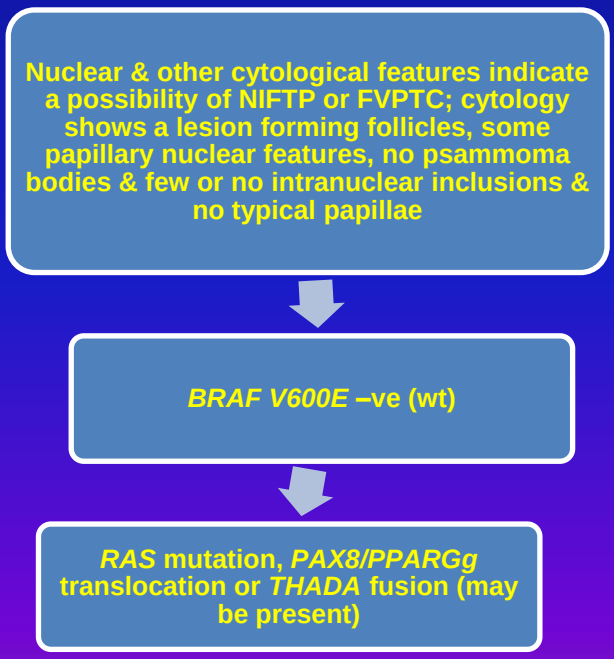
NIFTP lesions show a range of cytological features

Some may be reported as benign, others as TBSRTC Class III, Class IV, Class V & Class VI- the majority are class III, IV, or Class V on cytology

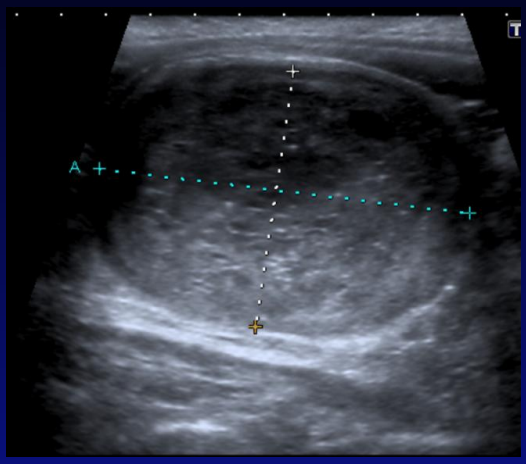
Preliminary reports suggest a risk of malignancy for TBSRTC Class VI will reduce from 97-99% to ~95% if NIFTP lesions are not regarded as malignant

Recent literature suggests that NIFTP FNA's show lack of classical papillae, few or no intranuclear inclusions & lack of psammoma bodies which may help to distinguish these lesions from classical type papillary carcinoma on FNA, Krane JF et al. Cancer Cytopathol 2016 Aug 26 doi: 10.1002/cncy.21769

NIFTP lesions never show BRAF V600E mutations and frequently show mutations typical of follicular thyroid tumours eg *RAS* mutations, or *PAX8/PPARG*γ rearrangements or THADA fusions. The algorithm below could be used to demonstrate a papillary or alternatively a follicular molecular phenotype to diagnose or exclude classical type papillary carcinoma & might assist in the differential diagnosis of NIFTP & classical type papillary carcinoma for UK Thy4 & UK Thy5 FNA's (TBSRTC Class V & VI FNA's)

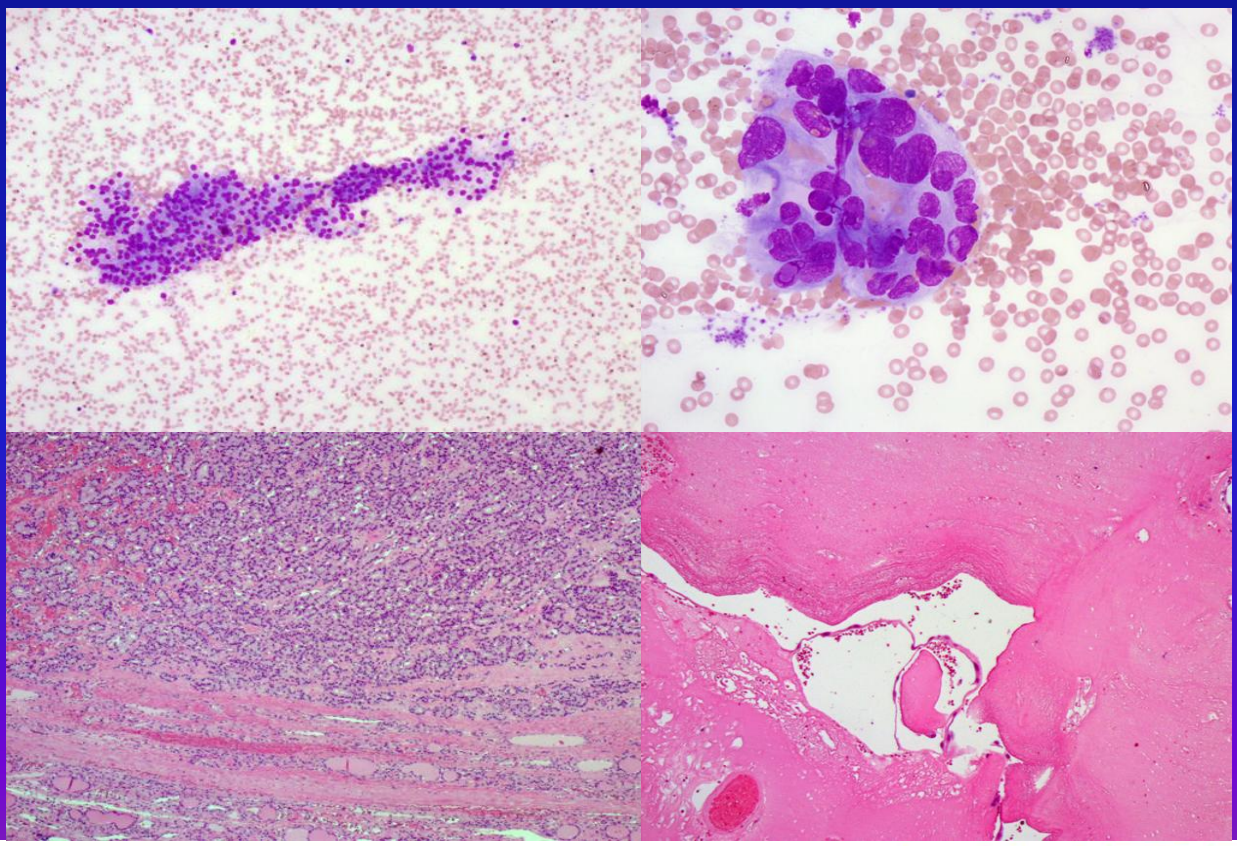


CN 1053/15 & CH18951/15 History
41 year old male, 42mm indeterminate nodule left thyroid, solid heterogeneous echotexture with a few tiny cystic clefts, no microcalcifications



Microscopic Findings

This is a comparatively low cellularity aspirate with sheets of follicular epithelial cells with colloid almost absent & focally with some nuclear atypia. This was reported as UK Thy 3F-neoplasm possible, TBSTRC class IV. A left thyroid lobectomy showed a minimally invasive follicular thyroid carcinoma, without vascular invasion



Diagnosis

Minimally invasive follicular carcinoma without vascular invasion, stage pT2.
The lesion shows also marked central necrosis/infarction in keeping with previous FNA

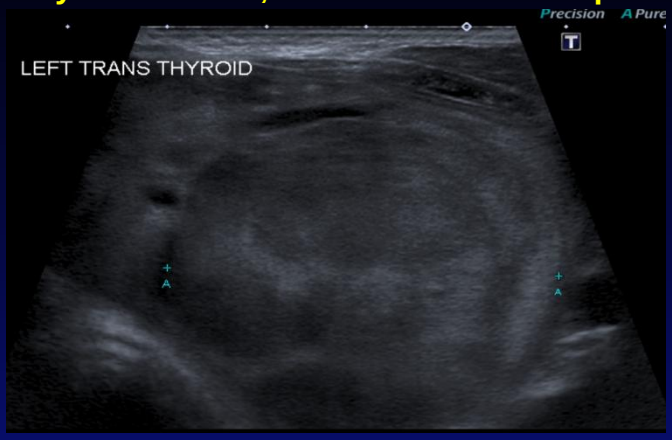
Learning Points

Infarction after FNA although typicalof oncocytic (Hurthle) cell lesions also occurs in non-oncocytic thyroid follicular neoplasms, both adenomas & carcinomas

Despite the relatively low cellularity the ultrasound appearances & cytological appearances & the lack of colloid indicates diagnosis of a follicular thyroid neoplasm in this case

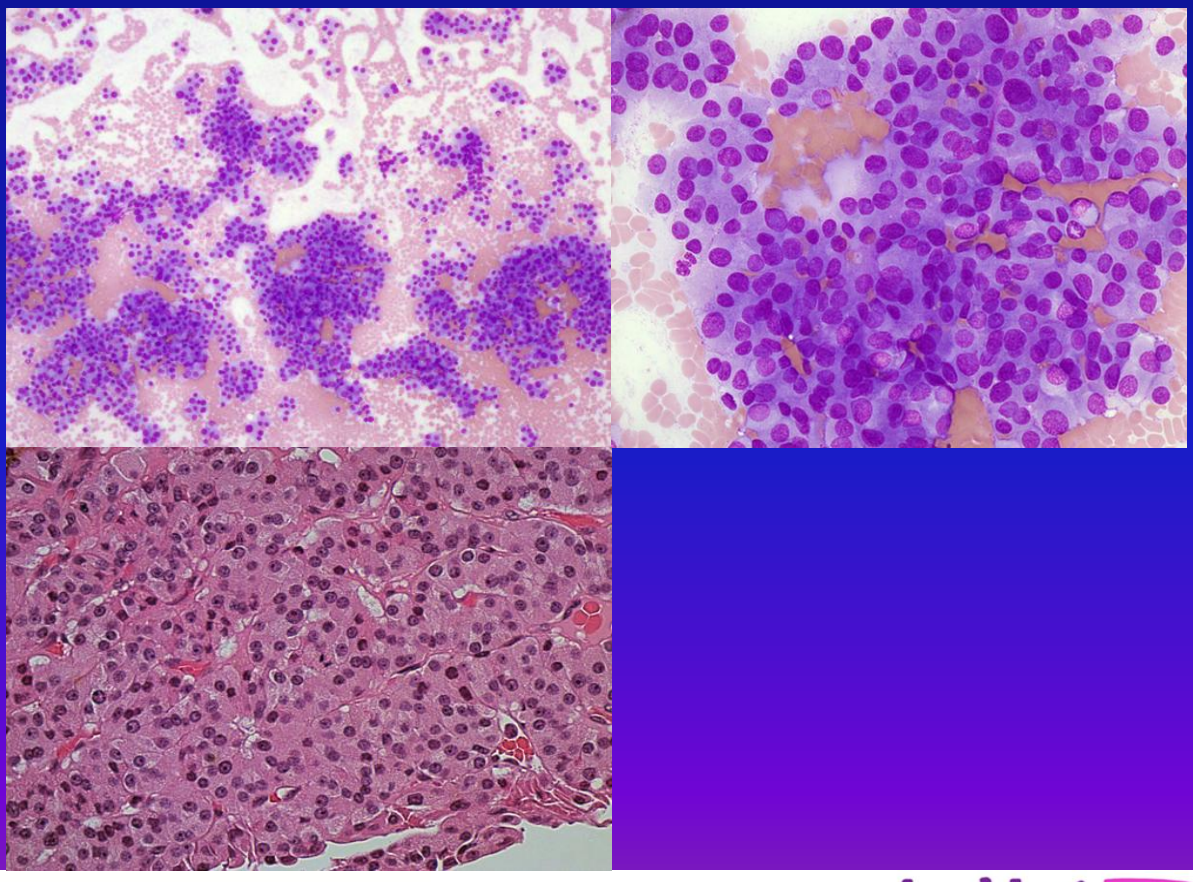
This case was BRAF V600E –ve (wild type) as would be expected in a follicular thyroid tumour

CN 1001/15 & CH18170/15 History
62 year old male, 40mm nodule lower pole left thyroid



Microscopic Findings

Sheets of follicular cells with little colloid with features of oncocytic (Hurthle) cells. This was reported as UK Thy3F-neoplasm possible equivalent to TBSRTC Class IV. This case showed no evidence of BRAF V600E mutation. A left thyroid lobectomy showed a minimally invasive follicular thyroid carcinoma of oncocytic type with at least 2 foci of capsular invasion but no evidence of vascular invasion.



Diagnosis

Minimally invasive follicular carcinoma (oncocytic variant) without vascular Invasion, stage pT3, pN0

Learning Points

Oncocytic follicular neoplasms of the thyroid are relatively easy to diagnose on FNA cytology most of the time

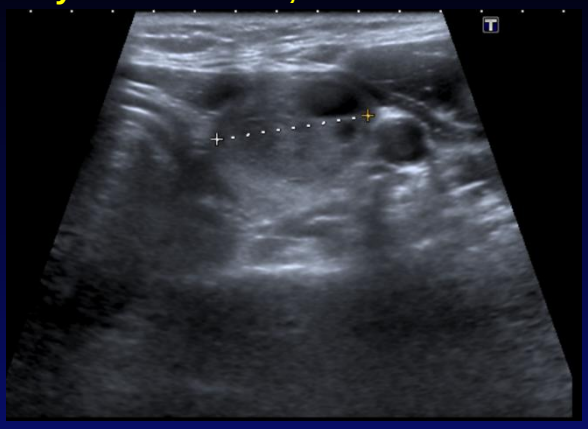
The differential diagnosis, oncocytic variant of papillary thyroid carcinoma is rare and shows different nuclear features to oncocytic follicular neoplasms

Some papillary thyroid carcinomas show eosinophilic cytoplasm, characteristic of a BRAF V600E mutated phenotype but the nuclear features are totally different to those seen in oncocytic follicular thyroid lesions

The majority of oncocytic variants of papillary thyroid carcinoma show BRAF V600E mutations so in a difficult case BRAF V600E testing may be helpful

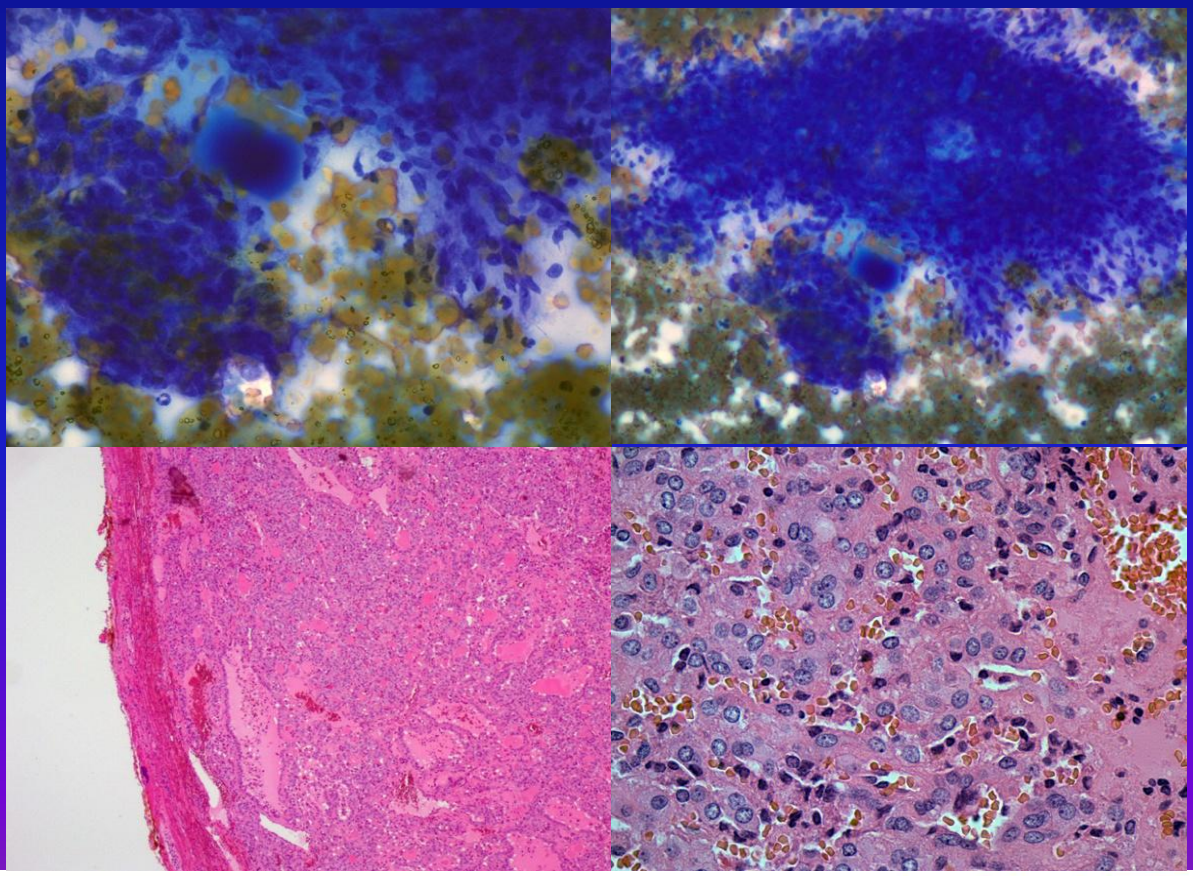
In our experience we have seen a false positive diagnosis of malignancy in a benign oncocytic neoplasm of the thyroid when there was air drying or smearing artefact, hence high quality well prepared slides are essential

CN 917/15 & CH66/16 History
45 year old female, dominant 31mm nodule left thyroid.



Microscopic Findings

Sheets of follicular cells with little colloid, and without nuclear features of papillary carcinoma. This was reported as UK Thy3F neoplasm possible equivalent to TBSRTC Class IV. A left thyroid lobectomy showed a follicular adenoma



Diagnosis

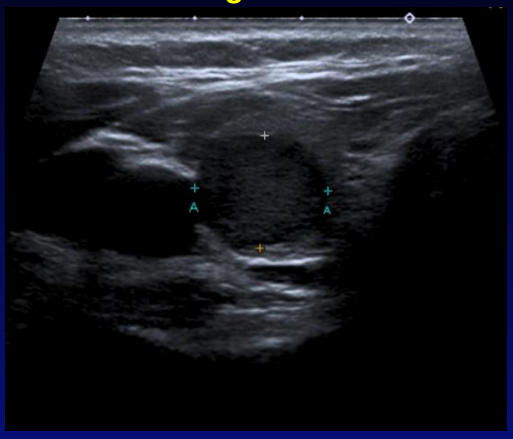
Follicular adenoma

Learning Points

The majority of aspirates with features such as this with cellular groups of follicular cells, forming follicles and without significant colloid will be from follicular adenomas although follicular carcinoma cannot be excluded hence the need to excise the nodule.

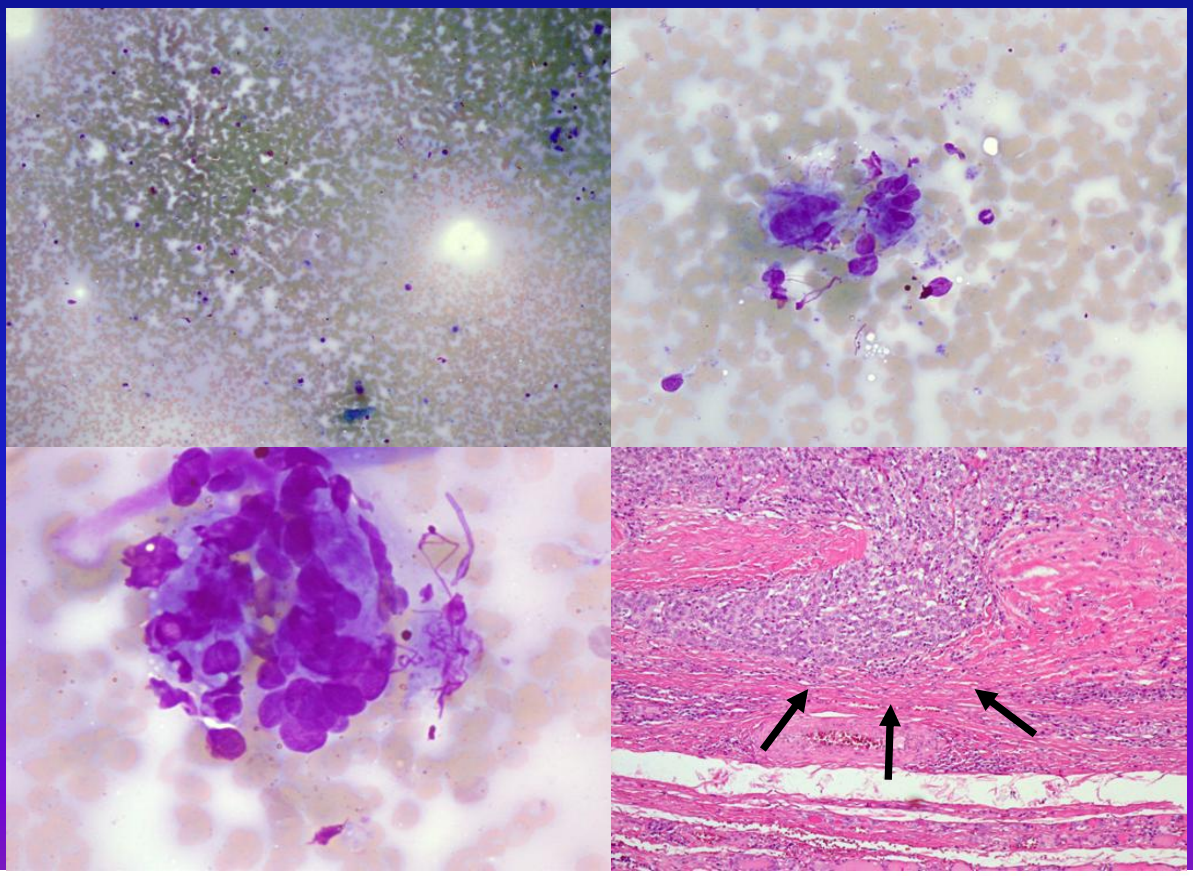
This case shows no significant nuclear atypia therefore NIFTP and FVPTC can be excluded cytologically

CN 821/15 & CH20274/15 History
62 year old female, multiple nodules in both thyroid lobes, largest in right lobe 32mm, well defined, hypoechoic, hypervascular, no calcification. Appearances of a multinodular goitre



Microscopic Findings

Poor quality very low cellularity FNA with very little cellular material, with a few clusters of cells, some degenerate & of uncertain significance, some minor atypia is present. Reported as UK Thy3a (neoplasm possible- focal nuclear atypia) TBSRTC Category III with a recommendation to repeat this FNA. Repeat FNA was UK Thy4 (TBSRTC Cat V) so total thyroidectomy was undertaken with level VI node dissection



Diagnosis

Minimally invasive follicular carcinoma, pT2 (m) with capsular & vascular invasion with 3 benign lymph nodes at level VI

Learning Points

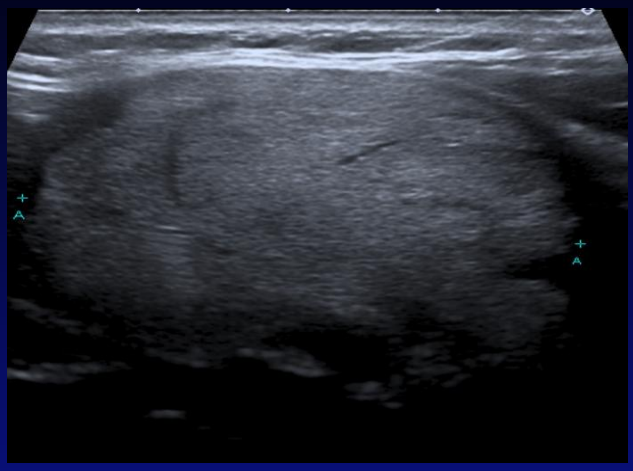
A low cellularity or poor quality FNA with minor atypia should be repeated

Molecular testing may help in some cases of Thy3a/Category III FNA but only in our experience if papillary carcinoma is suspected.

Molecular testing also requires sufficient cellular material, in this case there was insufficient cellular material for molecular testing.

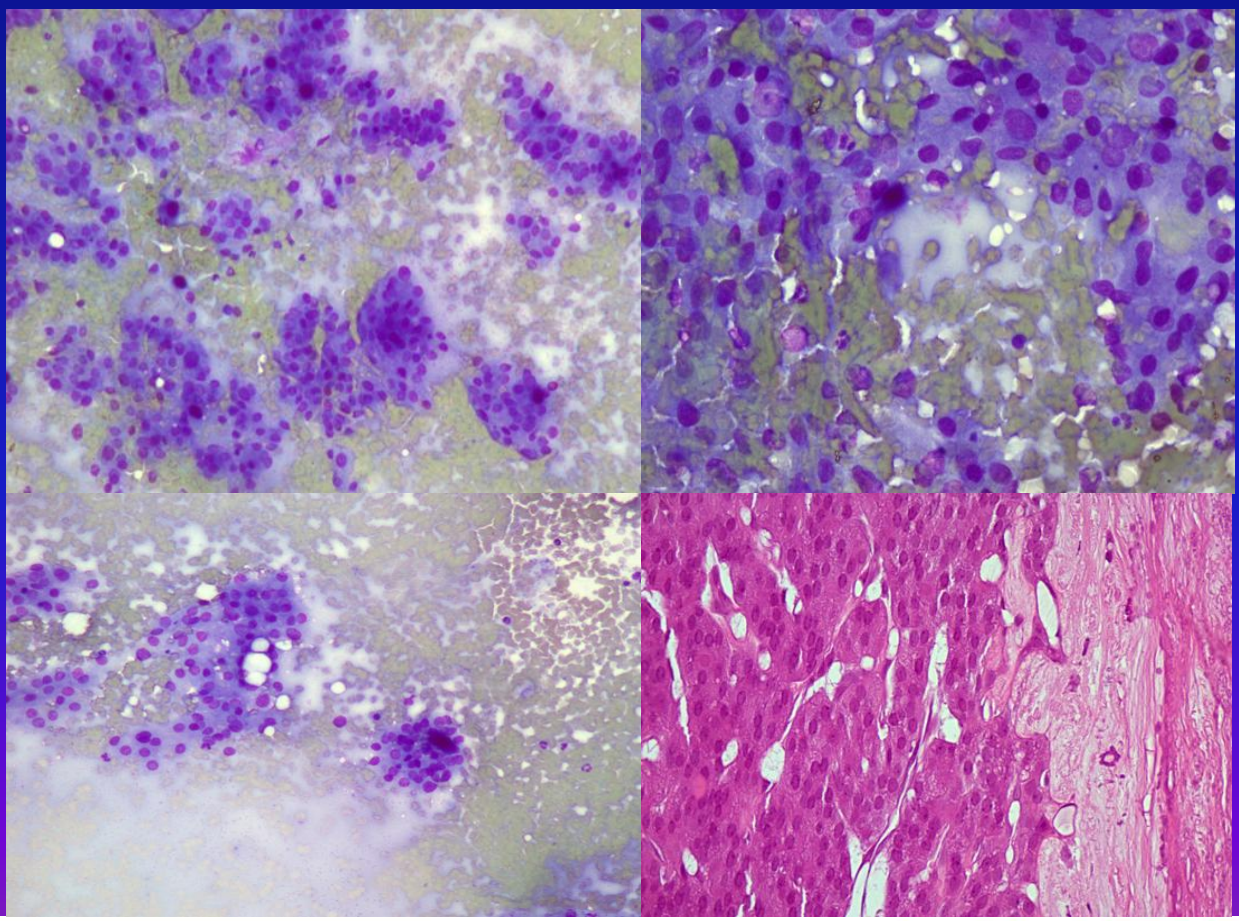
In this case repeating the FNA produced a result of Thy4 (suspicious for malignancy) equivalent to TBSRTC Category V and a total thyroidectomy was performed because the patient had a multinodular goitre and because of the relatively large nodule size showing a multifocal minimally invasive follicular carcinoma, pT2, with capsular and vascular invasion

CN 619/15 & CH 15277/15 History 66 year old female, 37mm large suspicious isoechoic solid lesion with marked central vascularity, internal heterogeneity and focal isoechoic areas



Microscopic Findings

Sheets of oncocytic (Hurthle) cells are present in this lesion which was reported as UK Thy3F neoplasm possible- oncocytic follicular neoplasm, equivalent to TBSRTC Class IV. This lesion was BRAF V600E –ve (wt)



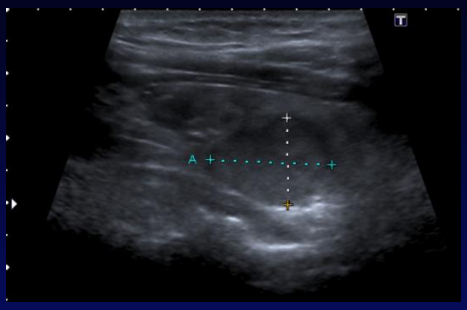
Diagnosis

Minimally invasive follicular carcinoma of oncocytic (Hurthle) cell type, 2 foci of capsular invasion but without vascular invasion, stage pT3

Learning Points

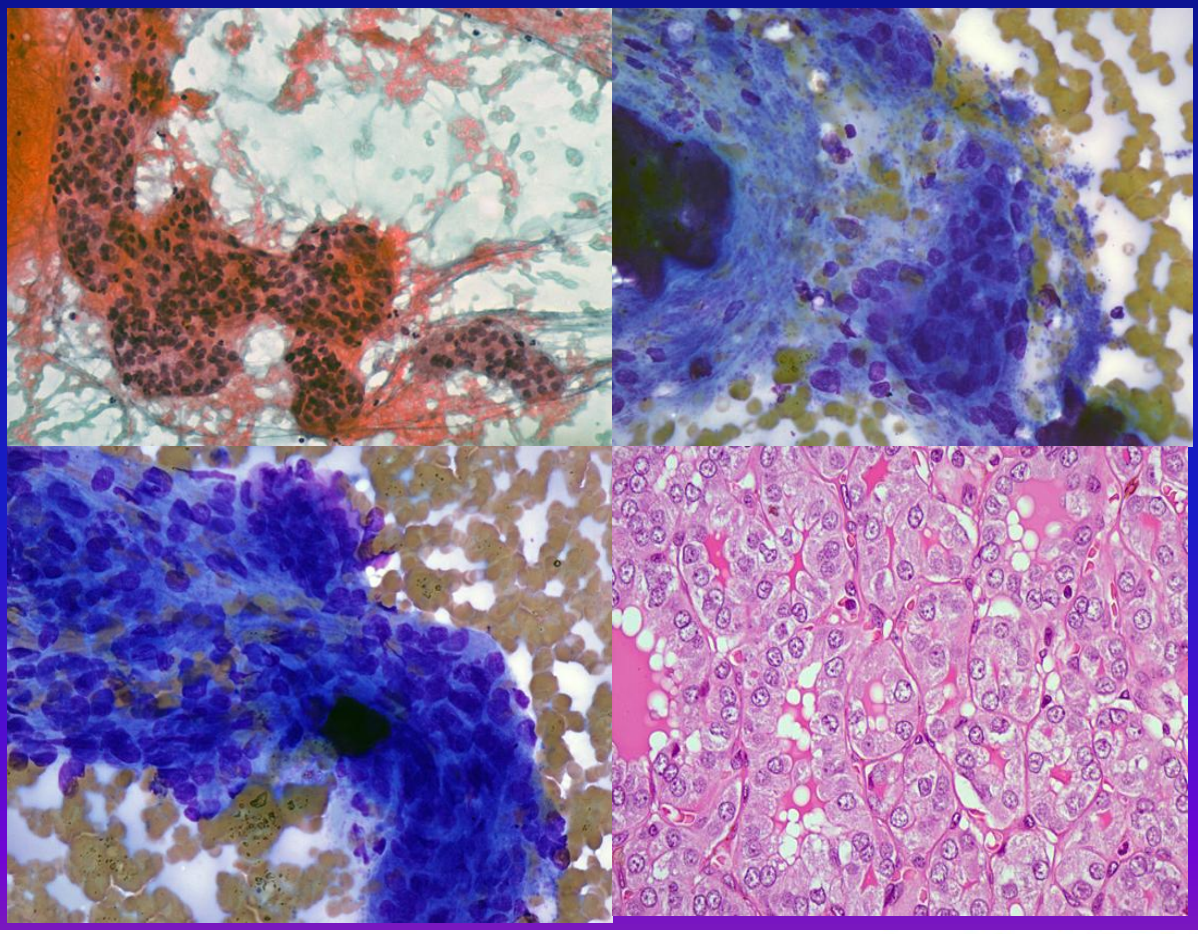
Typical oncocytic follicular neoplasm of the thyroid with a typical follicular molecular phenotype (BRAF V600E wt)

CN 340/15 & CH33740/15 History
64 year old female, solitary 19mm right midpole thyroid nodule, indeterminate ultrasound appearances



Microscopic Findings

Blood with groups & clusters of epithelial cells with nuclei raising the possibility of papillary carcinoma, also calcospherites, no evidence of BRAF V600E mutation, reported as UK Thy 3F (neoplasm possible- suggestive of a follicular neoplasm). In TBSRTC if the features were sufficiently developed this would be regarded as Category V suspicious of malignancy; suspicious for papillary thyroid carcinoma, if the nuclear features were not so well developed as Category III AUS



Diagnosis

Minimally invasive follicular variant of papillary carcinoma, pT1b (m) without vascular invasion

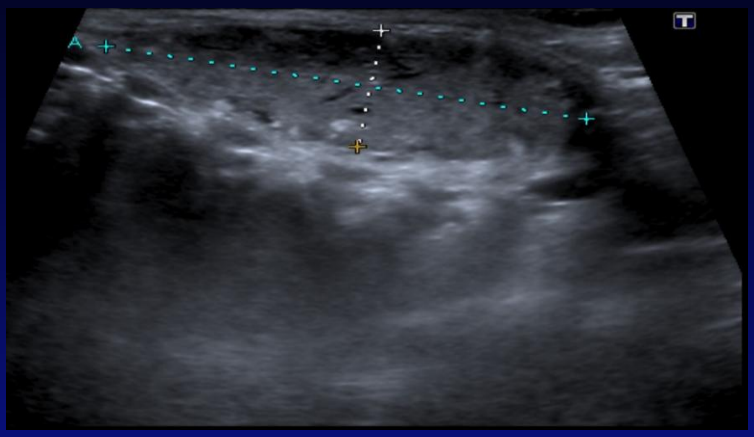
Learning Points

Follicular variant of papillary carcinoma (FVPTC) is often suspected on FNA cytology

Majority of FVPTC do not show BRAF V600E mutation in contrast to classical PC where BRAF V600E mutation is seen in 50-60%

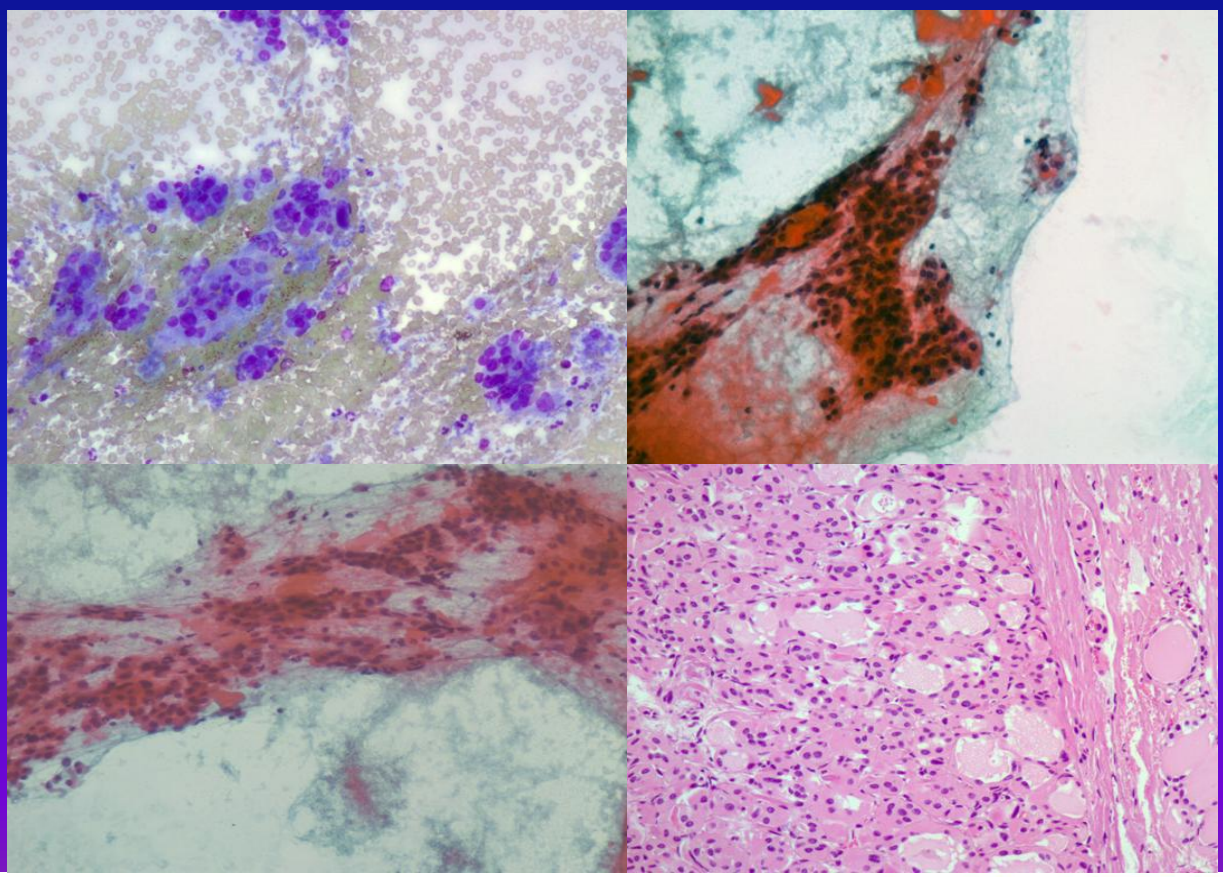
The cytological features of FVPTC e.g. follicles & lack of prominent papillae overlap with features of follicular adenoma in some cases, NIFTP, and classical papillary carcinomas

CN 2028/15 & CH35464/15 History
68 year old female, long standing thyroid nodule, also mucoepidermoid carcinoma excised right parotid gland. Multinodular goitre with 35mm U3 nodule in isthmus



Microscopic Findings

Most of the material is on the Papanicolaou stained smear showing sheets of follicular epithelial cells with small amounts of colloid & without nuclear atypia. This was reported as UK Thy 3f, equivalent to TBSRTC Class IV & an isthmusectomy was performed showing a follicular adenoma



Diagnosis

Follicular adenoma

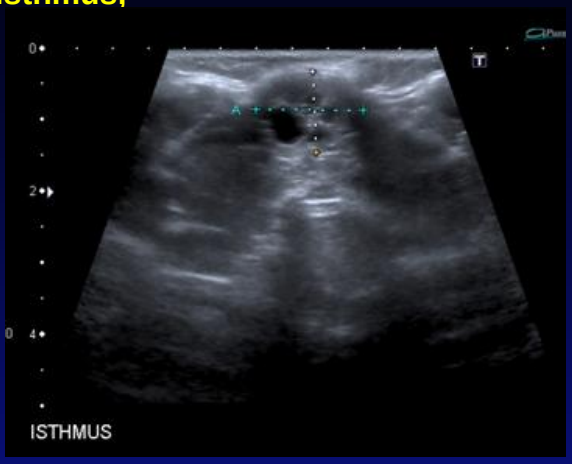
Learning Points

In this case there was little difficulty with the diagnosis cytologically & no features of mucoepidermoid carcinoma are seen.

Thyroid FNA after previous surgery can sometimes be problematic, particularly if patients have received radio-iodine or have received radiotherapy to the neck as this can cause problems with nuclear atypia on FNA cytology. Other lesions other than recurrent tumour that can cause diagnostic problems seen after previous surgery to the neck include post operative spindle cell nodule & suture granulomas

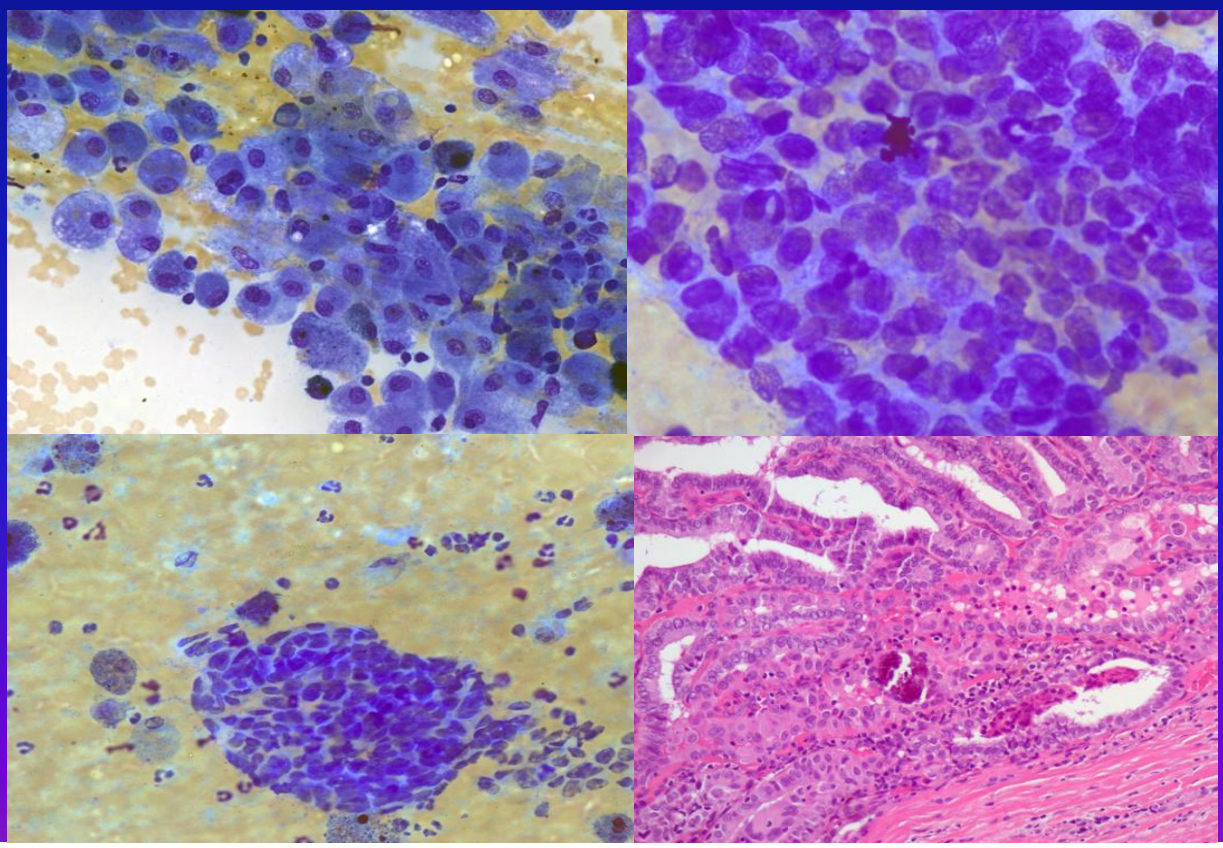
Primary mucoepidermoid carcinoma (MEC) of the thyroid is extremely rare but it does occur. In this patient's case the MEC arose in the right parotid gland

CN 1931/15 & CH35258/15 History
58 year old female, U3 part cystic, part solid vascularised nodule within isthmus,



Microscopic Findings

The aspirate findings are in keeping with a cyst, with a background of amorphous material & macrophages. There are also some groups of epithelial cells with nuclear atypia, with hyperchromatism & pleomorphism & elongated nuclei which imply that papillary carcinoma should be considered in the differential diagnosis. This was repprted as Thy3a-neoplasm possible & a 2nd FNA showed similar appearances. An isthmusectomy was performed, followed by completion thyroidectomy. Thy3a is broadly equivalent to TBSRTC Class III.



Diagnosis

Classical type papillary carcinoma (PTC). Within the isthmus was a 25mm PTC pT2 which was largely cystic, there was no vascular invasion

Learning Points

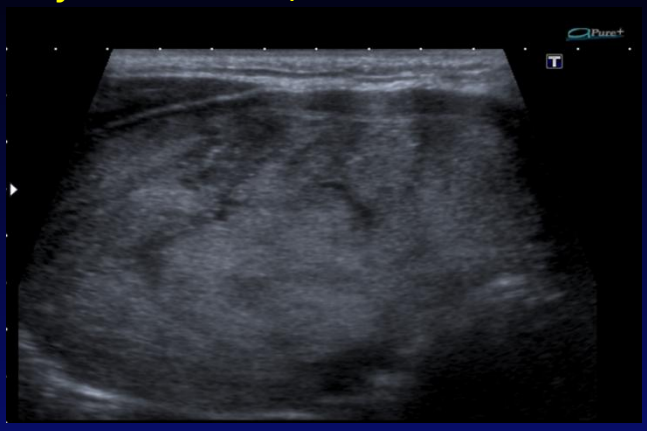
Papillary carcinomas are often cystic & degenerate & epithelial cells from a papillary carcinoma which is cystic can be mistaken for degenerate cyst lining cells.

Within the TBSRTC Class III category, the highest risk for malignancy in published series is from those FNA's which show atypia as a significant number of Class III FNA's with atypia turn out to be papillary carcinomas; in some series up to ~50% with turn out to be cancers Renshaw A, Cancer Cytopathol. 2011 Oct 25;119(5):322-7.

This case perhaps with hindsight should have proceeded directly to surgery because of the relatively high risk of malignancy associated with the nuclear atypia in this case

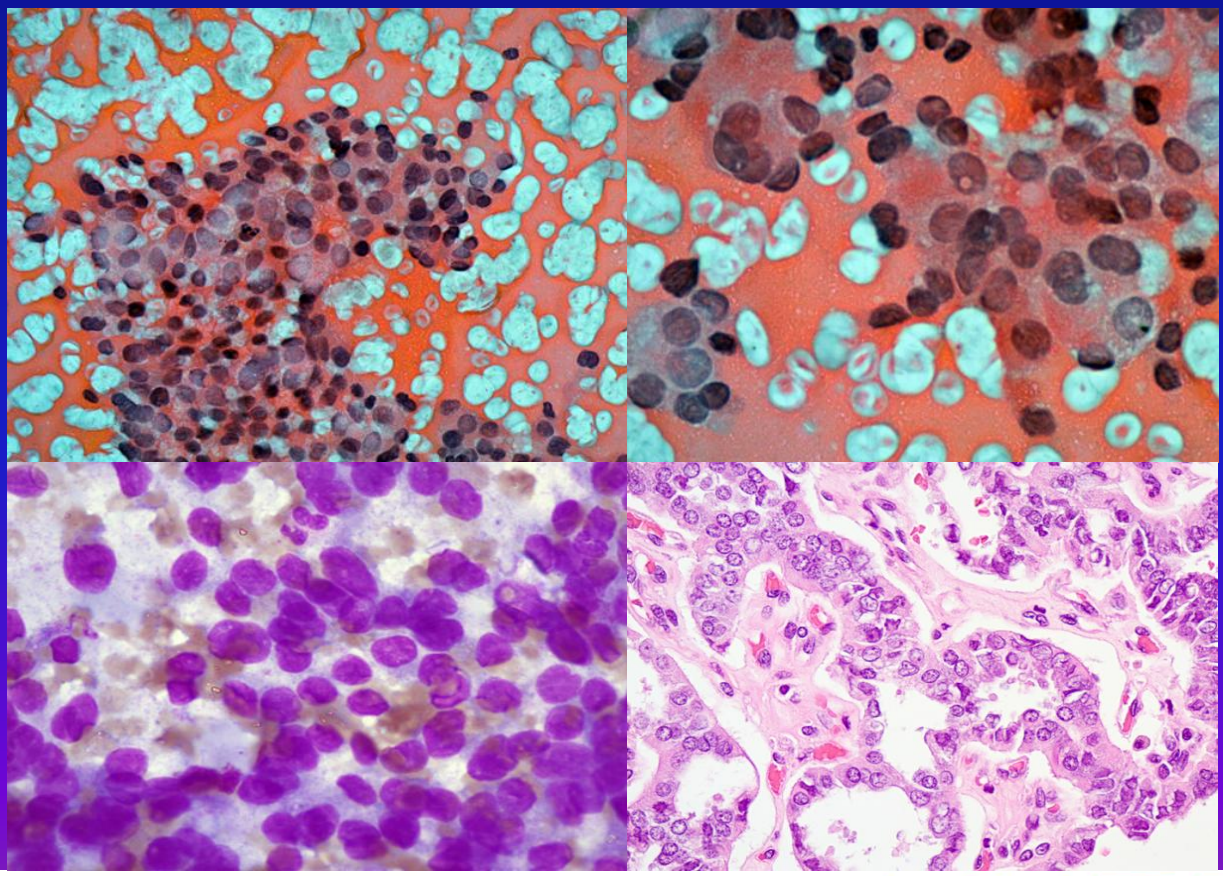
BRAF V600E mutational analysis might have been helpful in this case but it was not performed

CN 1628/15 & CH27116/15 History
35 year old female, isoechoeic 50mm standing thyroid nodule



Microscopic Findings

Sheets of thyrocytes with nuclear grooves, frequent inclusions & hyperchromatic nuclei typical of papillary thyroid carcinoma. This was reported as UK Thy 3F – neoplasm possible which is broadly equivalent to TBSRTC Class IV, however in this case given the papillary nature of the nuclei this would fall into TBSRTC category V. This case was BRAF V600E –ve (wild type).



Diagnosis

Follicular variant of papillary thyroid carcinoma (FVPTC).

This case was 45mm in size, pT3 & showed capsular invasion but no vascular invasion

Learning Points

In this case the presence of papillary nuclear features on cytology was noted but it was felt that there was insufficient evidence for a diagnosis of malignancy, UK Thy5, TBSRTC Class VI or UK Thy4 suspicious for malignancy, equivalent to TBSRTC Class IV.

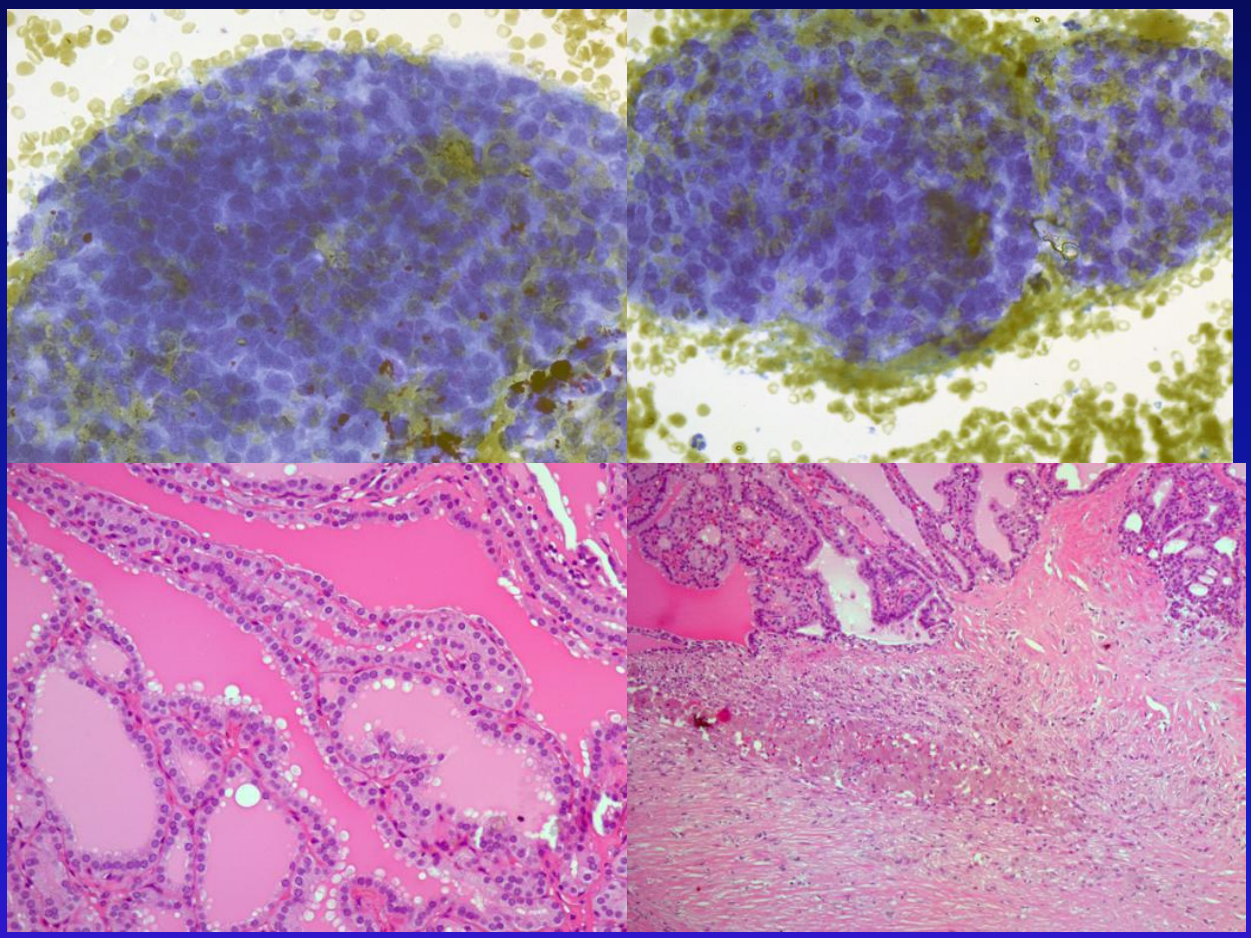
With hindsight this case probably should have been diagnosed as UK Thy4 - suspicious for malignancy.

The presence of large numbers of intranuclear inclusions and papillae on cytology in this case excludes a diagnosis of NIFTP with a very high level of confidence, despite the absence of a BRAF V600E mutation (BRAF V600E wt)

CN 14/15 & CH20955/15 History
22 year old female, 28mm hypervascular nodule right thyroid with mutliple other nodules, thyrotoxicosis

Microscopic Findings

This is a very low cellularity aspirate comprising a few single sheets of thyrocytes with some minimal nuclear atypia, without colloid, & without features of papillary thyroid carcinoma.



Diagnosis

Minor nuclear atypia in a patient with a partially cystic toxic adenoma

Learning Points

The minimal abnormal nuclear changes are attributed to thyrotoxicosis with a final working diagnosis of a partially cystic toxic adenoma of the right thyroid gland.

This was the 2nd UK Thy 3a aspirate from this patient, Thy3a is equivalent broadly to TBSRTC Class III FNA, hence the decision to excise the nodule.

Atypical benign thyrocytes may be due to thyrotoxicosis, and may occur after carbimazole therapy, radiation to the neck, or may be seen with other drugs, as well as in conditions such as congenital dyshormonogenetic goitre.

Another diagnostic pitfall is the atypia often seen in cyst lining cells in thyroid cysts